Seizure 23 (2014) 819–824

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Review

Ehlers–Danlos syndrome: A cause of epilepsy and periventricular heterotopia

Alberto Verrotti [a], Debora Monacelli [a], Miriam Castagnino [a], Maria Pia Villa [b], Pasquale Parisi [b,*]

[a] Department of Pediatrics, University of Perugia, Perugia, Italy
[b] Child Neurology, NESMOS Department, Chair of Pediatrics, Faculty of Medicine and Psychology, Sapienza University c/o Sant'Andrea Hospital, Via di Grottarossa, 1035-1039, 00189 Rome, Italy

ARTICLE INFO

Article history:
Received 10 January 2014
Received in revised form 20 July 2014
Accepted 23 July 2014

Keywords:
Ehlers–Danlos syndrome
Periventricular heterotopia
Nodular heterotopia
Epilepsy

ABSTRACT

Purpose: Ehlers–Danlos syndrome (EDS) comprises a variety of inherited connective tissue disorders that have been described in association with various neurological features. Until now the neurological symptoms have not been studied in detail; therefore, the aim of this review is to analyze the possible association between EDS, epilepsy and periventricular heterotopia (PH).
Methods: We have carried out a critical review of all cases of epilepsy in EDS patients with and without PH.
Results: Epilepsy is a frequent neurological manifestation of EDS; generally, it is characterized by focal seizures with temporo-parieto-occipital auras and the most common EEG findings epileptiform discharges and slow intermittent rhythm with delta–theta waves. Epilepsy in EDS patients is usually responsive to common antiepileptic therapy; very few cases of drug resistant focal epilepsy requested surgical treatment, with favorable results in terms of outcome. Epilepsy is the most common presenting neurological manifestation associated with PH in EDS patients. Abnormal anatomic circuitries (including heterotopic nodules) could generate epilepsy in patients with PH.
Conclusion: Among the principal neurological manifestations, epilepsy and PH have a considerable importance and can influence the long-term evolution of these patients. We hypothesize that PH may determine the epileptic manifestations in patients with EDS; much remains to be learnt about the relationships between nodules and the epileptic manifestations in EDS syndrome.

1. Introduction

Ehlers–Danlos syndrome (EDS) includes a group of hereditary connective tissue disorders (genetics defects affecting the biosynthesis and structure of collagen type I, III and V), mainly characterized by joint hypermobility, skin fragility, hyperextensibility and easy bruisability.[1–7] It may also presents neurological features such as disease of the cerebrovascular system, peripheral neuropathy, plexopathy, chronic pain syndrome, spontaneous intracranial hypotension, polymicrogyria, subependymal periventricular heterotopias and epilepsy.[8–13] The spectrum of severity of these manifestations is variable, ranging from very mild findings to severe debilitating disorder.[14]

Some patients may develop different types of epileptic conditions, i.e. generalized or partial seizures, with different EEG abnormalities.[13–16]

In this review, we analyze the main types of epilepsy reported in patients affected by EDS and the neurologic aspects of periventricular heterotopia (PH).

2. Classification

The current Villefranche Classification of EDS (1997) recognizes six subtypes based on phenotype, inheritance pattern and underlying biochemical and molecular defects.[2] The most common subtypes of EDS are the classic, hypermobility and vascular subtypes while kyphoscoliosis, arthrochalasis and dermatosparaxis types represent very rare conditions.[17] This classification is very important in terms of management and counseling to the patients and their families.

* Corresponding author at: Child Neurology, Headache Paediatric Center, Paediatric Sleep Disorders, Chair of Paediatrics, NESMOS Department, Faculty of Medicine & Psychology, Sapienza University, c/o Sant'Andrea Hospital, Via di Grottarossa, 1035-1039, 00189 Rome, Italy. Tel.: +39 6 33775971; fax: +39 6 33775941.
E-mail addresses: pasquale.parisi@uniroma1.it, parpas@iol.it (P. Parisi).

http://dx.doi.org/10.1016/j.seizure.2014.07.014
1059-1311/

Table 1
Ehlers–Danlos syndrome classification.

EDS subtypes (old name)	Inheritance	Genetic defects	Major symptoms
Classic (I/II)	AD	COL5A1, COL5A2,	Skin hyperextensibility, widened atrophic scars Joint hypermobility, muscle weakness, distal contractures
Hypermobility (III)	AD	Unknown	Generalized hypermobility and subtle skin findings
Vascular (IV)	AD	COL3A1	Arterial rupture at a young age
Vascular-like	AD	COL1A1	Features of both classic and vascular type
Cardiac-valvular	AR	COL1A2	Mild skin, joint hypermobility, hypotonia, osteopenia (in childhood); valve disease (in adulthood)
EDS with periventricular heterotopia	X-linked recessive	FLNA, ARFGEF2	Nodular brain heterotopia and classic EDS symptoms
Kyphoscoliosis (VIa)	AR	Lysyl-hydroxylase (PLOD1)	Early progressive kyphoscoliosis
Muscolocontractural (VIb)	AR	CHST14	Craniofacial abnormalities, joint contracture, hypotonia, gastrointestinal and genitourinary problems
Arthrocalasia (VIIa/VIIb)	AD	COL1A1, COL1A2	Congenital bilateral hip dislocation
Dermatosparaxis (VIIc)	AR	ADAMTS2	Sagging skin, eye lid edema, short stature and fingers
Periodontal (VIII)	AD	12p13	Severe early periodontitis
Spondylocheirodysplastic	AR	SLC39A13	Short stature and mild skeletal dysplasia
EDS-osteogenesis imperfecta	AD	COL1A1, COL1A2	Bone fragility and classic EDS symptoms
Brittle cornea syndrome	AR	ZNF469 PRDM5	Ocular fragility and keratoconus
Progeroid EDS	AR	B4GALT7	Wrinkled face, curly fine hair, periodontitis
Tenascin X deficient	AR?	TNXB	Joint hypermobility, hyperextensible and sleeve-like character to skin, marked bruising, normal scarring
FKBP14 related	AR	FKBP14	Marked kyphoscoliosis, hearing loss, myopathy, short stature, joint hypermobility

Adapted from De Paepe and Malfait[17] and from Karaa and Stoler.[20]
AD: autosomal dominant and AR: autosomal recessive.

During the last years, the clinical and molecular definition of several new EDS variants called for an enrichment of the classification (Table 1) because EDS pathogenesis may be influenced by genetic defects involving the biosynthesis of other extracellular matrix molecules components and processes[18–21]; furthermore, many patients cannot be categorized into a subtype because clinical manifestations are ambiguous.

In Classic type of EDS, the mutations in type V collagen include heterozygous nonsense, frameshift or splice-site mutations in COL5A1; these mutations introduce a premature stopcodon elicit nonsense-mediated decay of the mutant mRNA, and hence no abnormal protein is produced. As such, the result is diminished production of alpha1-chains of type V collagen.[22,23]

EDS hypermobility type (EDS-HT) is considered an autosomal dominant trait with incomplete penetrance, variable expressivity and influenced by sex; in contrast to the other EDS variants, the genetic defect of this type is still unknown[24]; haploinsufficiency for Tenascin-X was found in some patients affected by hypermobility type of EDS (EDS-HT).[25]

EDS vascular type is an autosomal dominant disorder caused by mutations in gene COL3A1 coding for type III procollagen synthesis. The type III procollagen is predominantly distributed in the skin and walls of blood vessels; mutations in gene COL3A1 may lead to spontaneous arterial, intestinal or uterine rupture, with consequent premature death.

The EDS kyphoscoliotic type is an autosomal recessive disorder caused by mutations of PLOD1 gene, that encodes lysyl hydroxylase-1; this enzyme is involved in the formation of intermolecular crosslinks that provide stability to the collagen fibrils.[17]

Mutations in CHST14, encoding dermatan-4-sulfotransferase-1, cause a deficiency of dermatan sulfate (DS) which results in impaired decorin-mediated collagen fibril assembly and tissue fragility. This type of EDS is defined musculocontractural.[19,26,27] Mutations of this gene can be present also in patients with another subtype called EDS VIB-brittle cornea syndrome: this autosomal recessive condition, is also determined by ZNF469 gene and by PRDM5 gene mutations.

EDS arthrocalasia type (formerly types arthrocalasia A and B), an autosomal dominant form, is very rare: this type is caused by a defective processing of type I collagen synthesis. EDS type arthrocalasia A is determined by a disruption of procollagen chain $\alpha 1$(I), encoded by COL1A. EDS type arthrocalasia B is due to the abnormality of $\alpha 2$(I), procollagen chain encoded by COL1A2, and result in exon 6 skipping or genomic deletion of exon 6 COL1A2 gene.[28–30]

The dermatosparaxis type of EDS is very rare (only 10 or 11patients have been reported) autosomal recessive condition caused by abnormalities in ADAMTS2, which encodes for an N-proteinase involved in the ablation of N-propeptides whose cleavage is essential for complete maturation of collagen I.[24]

There are many other subtypes that have recently been identified that are caused by defects in non-collagenous genes that are involved in extracellular matrix organization.

Four EDS variants (arthrocalasia, classic with vascular rupture, cardiac-valvular, and EDS/osteogenesis imperfect overlap) are caused by dominant or recessive mutations in genes (COL1A1 and COL1A2) encoding the two chains of collagen type I with defect in structural proteins of collagen I. The mutations in type I collagen include missense mutations in COL1A1 that lead to the production of $\alpha 1$(I) dimmers.

The genetic etiology of another rare form of EDS associated with PH was established by recognition of the similarity of the neurology features with that of PH due to FLNA mutations.[31] Mutations conferring loss of function at the FLNA (encoding Filamin A) locus lead to X-linked periventricular nodular heterotopia (XL-PH).[32] To date, this is the only confirmed X-linked form of EDS. Recently, Reinstein et al.[33] have suggested that there is little molecular or clinical justification for considering EDS-PH as a separate entity from XL-PH, but instead they proposed that there is a spectrum of vascular and connective tissues anomalies associated with this condition for which all individuals with loss-of-function mutations in FLNA should be evaluated.

3. Clinical manifestations

EDS displays skin hyperextensibility and fragility, soft velvety skin, delayed wound healing atrophic scarring, joints hyperlaxity, dislocations, pain easy bruising, soft connective tissue fragility with possible involvement internal organs.

The autosomal dominant classic type of EDS is diagnosed by the presence of the three major criteria: joint hypermobility, hyperextensible skin and widened atrophic scars. In the group

of minor criteria are included the following manifestations: muscle hypotonia, velvety skin, easy bruising and the characteristic facial features (epichanthic folds, dilated scars on the forehead, excess skin over the eyelids).[17]

EDS hypermobility type (EDS-HT) is defined by the association of generalized joint hypermobility, widespread musculoskeletal pain and skin features like extensibility and smooth and velvety skin.[24]

Vascular type of EDS is characterized by excessive bruising and tendency to hematomas. The skin is not hyperextensible, but thin and translucent. These patients have a characteristic facial appearance, with a thin delicate nose, thin lips, prominent bones and milder laxity involvement. Although EDS vascular type has less striking clinical features, it is the most severe type. In fact, the vascular complications affected medium and large arteries: arterial rupture and dissections, aneurysmal degeneration or intracavitary bleeding are important complications.[34]

EDS kyphoscoliotic type is an autosomal recessive disorder characterized by early onset progressive kyphoscoliosis, severe neonatal muscular hypotonia, hyperextensible and bruisable skin, generalized joint hyperlaxity, osteopenia, scleral fragility and risk for rupture of ocular globe.[17,21]

Arthrochalasis type is characterized by severe joint hypermobility, skin hyperextensibility, bruisable skin, atrophic scars, muscular hypotonia, osteopenia, kyphoscoliosis and tissue fragility. The characteristic sign of this EDS type is congenital bilateral hip dislocation[28] and, rarely, cardiac involvement.[35]

Dermatosparaxis type of EDS is characterized by pronounced skin fragility and a redundant appearance of the skin.[24]

EDS cardiac-valvular type presents in childhood with mild skin and joint hypermobility, osteopenia, muscular hypotonia and is complicated in adulthood by severe cardiac valve insufficiency.

The rare form of EDS, called "Brittle Cornea Syndrome", is mainly characterized by ocular fragility, blue sclera and keratoconus (associated with skin and joint hypermobility and kyphoscoliosis).

The patients affected by the spondylocheirodysplastic form of EDS show moderate short stature, skeletal dysplasia, hypermobility of the small joints, hyperextensible thin skin, easy bruising, bluish sclera.[17]

In the EDS-PH, seizures constituting the most common clinical manifestation; vascular dilatation (mainly the aorta), joint hypermobility and variable skin findings are also associated anomalies.

Tenascin X-deficient EDS is distinguished from classical EDS by autosomal recessive inheritance, absence of abnormal scarring in the presence of profound joint hypermobility, very hyperextensible skin and striking bruising.[36,37] The presence of significant hypermobility in heterozygous carriers of null mutations suggested TNXB as a candidate gene in EDS type III, the hypermobile type, but wider screening failed to document mutations at sufficient frequency to account for EDS type III.

Progerioid EDS type is a new subtype of EDS characterized by wrinkled, loose skin on the face, curly fine hair, scanty eyebrows and eyelashes, in addition to the classical features of EDS.[29]

Periodontitis type of Ehlers–Danlos syndrome (EDS type VIII) is distinguished from other subtypes of EDS by severe periodontitis leading to premature loss of permanent teeth. The spectrum of skin manifestations includes skin hyperextensibility, easy bruising, pretibial discoloration, dystrophic scar formation. The skeletal phenotypes include joint laxity and dislocations, Marfanoid habitus, osteopenia, early-onset osteoarthritis, pectus deformity, scoliosis and pes planus.[33]

4. EDS and epilepsy

EDS may be accompanied by congenital or acquired central nervous system disorders and epilepsy.[10] The frequency of the EDS patients who suffer from epilepsy is not known.

In literature, there are no data about a possible higher prevalence of epilepsy in patients with EDS; probably, in patients with EDS there is a higher prevalence of epilepsy: in fact, in some patients a certain disruption in the link between the extracellular matrix and cytoskeleton with consequent malformations of the vessels and brain parenchyma can contribute to seizures; moreover, it is probable that those patients with structural abnormalities of central nervous system (such as PH) can suffer from epilepsy.

We report and analyze all cases of epilepsy in EDS patients with and without PH.

In most cases, epilepsy begins in childhood with focal seizures (especially in temporal areas). The most common EEG findings were interictal epileptiform discharges, slow intermittent rhythm with delta–theta waves.

The first EDS patient who presented epilepsy was described by Herrero in 1972.[9]

Some years later, Cupo et al. described a female patient, 30 years old, with EDS and grand mal seizures beginning at the age 21 years; she presented cerebral heterotopias with peculiar vascularization, that probably caused the seizure disorder. She died for myocardial infarction (aneurysm of the sinuses of Valsalva).[38]

Thereafter, Pretorius in 1983 described a female, 22 years old, affected by EDS type 1, presenting partial seizures that began generalized.[12]

Another patient with generalized epilepsy was described by Herrero in 1995: conventional antiepileptic drugs (AEDs) appeared to be ineffective; however, the newer AEDs had a positive effect.[9] Also another author[10] reported cases with seizures onset in childhood: these patients presented partial seizures except two who suffered from grand mal.

In 2000, Echaniz–Laguna described two cases: one 29 years old male patient had partial seizures that began at the age of 10 years; EEG showed left fronto-central area sharp-wave discharges that rapidly diffused over the two hemispheres, well controlled by carbamazepine treatment. The other patient showed generalized epilepsy, diffuse spike-waves at EEG and polymicrogyria; after treatment with anterior callosotomy there was a reduction of frequency and severity of seizures.[39]

Another important study[40] reported 7 news epileptic patients; all these patients showed bilateral nodular heterotopia (PNH) suggesting an association between epilepsy and this cerebral malformation.

Among the family studies, it is important to report the clinical and genetic analysis of a Spanish family in which three women suffered from EDS; a female patient had a history of spontaneous luxation since childhood and complex partial epilepsy followed by secondarily generalized tonic–clonic seizures since the age of 20 years. EEG showed temporal slow waves and MRI showed bilateral PNH. Also her daughter, from the age of 14 years had recurrent knee dislocations without seizures; her brain MRI revealed bilateral PNH and mega cisterna magna. The third case was an affected 19 years old woman (daughter of second patient) with a history of recurrent patellar dislocation, joint hypermobility, soft rubbery skin; at age of 18 years showed generalized epilepsy; she had PNH and mega cisterna magna.[15]

Twenty-two EDS patients were reported in our review: 17/22 patients (77.3%) were female, 4/22 patients (18.2%) were male, in one case (4.6%) was not reported the sex of the patient. Epilepsy started in childhood in 8/22 patients (36.4%), after 9 years of age in 10/22 patients (45.5%), while in 4/22 cases (18.2%) was not reported the age of epilepsy onset. The population consisted of the following types of EDS: one patient (4.6%) was affected by EDS type I, 3/22 patients (13.7%) by type III, 3/22 patients (13.7%) by type IV; 2/22 patients (9.1%) by type IX; in 2/22 cases (9.1%) were not sure the type of EDS (in Table 1, the patient number 8 and the patient

Table 2
Pertinent data of the studies examined.

Case	Reference	Sex/age (yr)	EDS type	Age of onset of epilepsy	Type of seizures	EEG patterns	Therapy	Follow-up	PH
1	Herrero, 1972	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
2	Cupo, 1981	F, 30	N.A.	21 years	Grand mal	Right temporal focal seizures discharges	N.A.	Died for myocardial infarction (aneurysm of the sinuses of Valsalva)	Yes
3	Pretorius, 1983	F, 22	I	11 years	Partial and generalized	N.A.	N.A.	N.A.	Ectopic gray matter
4	Thomas, 1996	F, 24	N.A.	14 years	Partial	Isolated slow spike waves over the left frontocentral area	Phenobarbital 150–200 mg/day	Generalized szs when fenozolone was added to antiepileptic therapy	Yes
5	Jacome, 1999	M, 36	IX (OHS)	Childhood	Partial	Bilateral Theta slowing	Carbamazepine	Seizures free	N.A.
6	Jacome, 1999	M, 29	IX (OHS)	Childhood	Partial	Generalized sharp and slow wave complexes of frontal accentuation	Reduction of szs with combination of carbamazepine and valproate	Pseudosz improved with fluoxetine and psychotherapy	N.A.
7	Jacome, 1999	F, 70	IV	Grand mal szs during childhood	Partial	6-H posterior dominant rhythm. Excessive intermixed slow activity while awake; generalized theta burst	Carbamazepine and phenytoin.	Persistence of generalized epilepsy	N.A.
8	Jacome, 1999	F, 28	III (?)	Grand mal in childhood	Partial	Generalized sharp theta discharges	AEds	Poor control	N.A.
9	Jacome, 1999	M, 69	IV	46 years	Generalized and partial	Mild slowing of background in theta range	Valproate and phenytoin	N.A.	N.A.
10	Jacome, 1999	F, 35	IV	N.A.	Partial	Normal	Valproate	Szs free	N.A.
11	Jacome, 1999	F, 68	III or IV (?)	N.A.	Generalized	Normal	Phenobarbital	Szs free	N.A.
12	Echaniz-Laguna, 2000	M, 29	N.A.	10 years	Partial with secondary generalization	Left fronto-central area sharp-wave discharges that rapidly diffused over the two hemisphere	Phenobarbital, valproate carbamazepine	Szs free	N.A.
13	Echaniz-Laguna, 2000	F, 22	III	Childhood	Generalized szs	Generalized spikes	AEDs and anterior callosotomy	Reduction of frequency and severity of seizures after callosotomy	N.A.
14	Sheen, 2005	F, 7	N.A.	6	Single seizure	N.A.	N.A.	N.A.	Yes
15	Sheen, 2005	F, 24	N.A.	22	NA	N.A.	N.A.	N.A.	Yes
16	Sheen, 2005	F, 25	N.A.	17	Generalized (catamenial)	Excessive slow wave activity	N.A.	N.A.	Yes
17	Sheen, 2005	F, 53	N.A.	Epilepsy since childhood	N.A.	N.A.	N.A.	N.A.	Yes
18	Sheen, 2005	F, 18	N.A.	4	Partial	Multifocal sharp and spike waves	N.A.	N.A.	Yes
19	Sheen, 2005	F, 29	N.A.	14	Generalized	N.A.	N.A.	N.A.	Yes
20	Sheen, 2005	F, 15	N.A.	N.A.	Focal	N.A.	N.A.	N.A.	Yes
21	Gomez-Garre, 2006	F, 68	III	20	Partial szs with secondary generalization	Temporal slow waves	N.A.	N.A.	Yes
22	Gomez-Garre, 2006	F, 19	III	18	Generalized	N.A.	N.A.	N.A.	Yes

Abbreviations: SZS: seizure; PH: periventricular heterotopia; OHS: occipital horn syndrome; AEDs: antiepileptic drugs; NA: not available.

number 11). In the other cases (11 cases, 50%) the type of EDS was not mentioned. The large majority of patients presented partial seizures (8/22 patients, 36.4%), 5/22 (22.8%) generalized epilepsy, 2/22 (9.1%) had generalized and partial seizures, one patient (4.6%) presented grand mal; in two cases (9.1%) partial seizures with secondary generalization were reported and in 4 cases (18.2%) the characteristics of the epilepsy were missing. Four out of 22 patients received antiepileptic drug (AED) monotherapy while 6 patients (27.3%) were treated with polytherapy; in the other cases the treatment was not reported. At last follow-up, only 4 patients were seizure-free (the time of the follow-up is unknown).

5. EDS and periventricular heterotopia

PH includes a group of neuronal migration disorders characterized by clinical and genetic variability. Three main groups are described: PNH, subcortical heterotopia and marginal glioneural heterotopia.[41–43] Disorders affecting neuronal migration are characterized by abnormal neuronal positioning. When migration is impaired during later cortical development, abnormal cell position is more likely to be restricted to the cortex.[44–47]

The association of EDS with PH is difficult to explain. A disruption in the link between the extracellular matrix and cytoskeleton could cause an aberration in cellular migration during development with possible congenital malformations of the vessels and the brain parenchyma, including cortical dysgenesis.[40,48,49]

EDS is considered a disorder of the extracellular matrix related with a disruption in glycoproteins, involving collagen or proteoglycans or other extracellular matrix proteins like Tenascin-X.[36,50,51] Cells join to the extracellular matrix by integrins, whose intracellular portion binds to the actin filaments of the cytoskeleton. Filamin A (FLNA) links the beta-integrin cell adhesion receptors, but does not alter the formation of these focal adhesion sites and the extracellular matrix assembly.[52–56] Otherwise, FLNA mutations could decrease the connection of the cells to the extracellular matrix or compromise regulation to the cytoskeleton through the FLNA binding to integrins proteins.[49,57] Furthermore, a relationship between FLNA and collagen can have a role in the mechanism of platelet aggregation; in fact, mutations in the FLNA and in COL3A1 gene (vascular type of EDS) are both known to determine excessive bleeding, probably due to vascular fragility and platelet dysfunction[49,58]; mutations in FLNA can cause classic bilateral PNH,[59–64,32,65] and the inheritance can be X-linked dominant (mutations in the Filamin A gene) or autosomal recessive (mutations in ARFGEF2 gene).[40] This last mutation has been associated to PNH but in patients without EDS.

Most cases of patients with PH present epilepsy[66–71]; the type of seizures is variable, even if majority of patients have partial attacks with temporo-parieto-occipital aura, and the severity may range from mild (with remission without anticonvulsant therapy) to intractable epilepsy. Age of onset is also variable from first year of life to adolescence.[47,72–76] No correlation has been found between the extent and severity of the PH and frequency of seizures. It has been suggested that onset of seizures can begin simultaneously from periventricular heterotopic cortex and from distantly located cortical areas. In Table 2 we report the data of the EDS patients affected by epilepsy and PH.

Actually, no guidelines are described for the treatment and management of PH and its complications. In most cases, antiepileptic drugs are used to control seizures with good results.[72,76] For intractable focal seizures, surgical resection can be request.

6. Conclusions

EDS may affect central nervous system although not many cases of patients affected by EDS and epilepsy are reported; frequently, they show PH. It is possible that the nodules, the main lesions of PH, can determine the epileptic manifestations present in patients with EDS. A careful evaluation of patients may reveal asymptomatic and unrecognized abnormalities, which offer better explanations for the symptoms and must be considered for the prognosis.

EEG recording, neuroimaging and neuropsychological tests can help to define diagnosis and to have a better care for people affected by EDS and epilepsy. It is important to reach a clearer understanding of the possible mechanisms underlying epileptic disorder, to improve therapy and long-term outcome of these patients.

Financial disclosure

The authors have no financial relationships to disclose with regard to this article.

Conflict of interest statement

We declare we have no financial interest.

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